ACCESSION NUMBER: 95012875 MEDLINE
DOCUMENT NUMBER: 95012875 PubMed ID: 7927925
TITLE: The tyrosine kinase activity of the C-erbB-2 gene product (p185) is required for growth inhibition by anti-p185 antibodies but not for the cytotoxicity of an anti-p185-ricin-A chain immunotoxin.
AUTHOR: Xu F J; Boyer C M; Bae D S; Wu S; Greenwald M; O'Briant K; Yu Y H; Mills G B; Bast R C Jr
CORPORATE SOURCE: Department of Medicine, Duke University Medical Center, Durham, NC 27710.
CONTRACT NUMBER: CA 39930 (NCI)
SOURCE: INTERNATIONAL JOURNAL OF CANCER, (1994 Oct 15) 59 (2) 242-7.
Journal code: 0042124. ISSN: 0020-7136.
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AB Our previous studies have demonstrated that 7 of 10 IgG antibodies against distinct epitopes on the extracellular domain of the c-erbB-2 gene product (p185) inhibit the anchorage-independent growth of SKBr3 human breast-cancer cells that overexpress this transmembrane tyrosine kinase growth-factor receptor. Two of 7 growth-inhibitory antibodies also block the binding and function of the gp30 and p75 c-erbB-2 ligands. In this report we have studied phosphorylation of p185 and different intracellular substrates after binding of antibodies that do or do not inhibit tumor-cell growth. A correlation has been found between antibodies that inhibit growth and the intensity of tyrosine phosphorylation of p185. At late intervals, serine phosphorylation of at least 3 intracellular substrates is increased preferentially by growth-inhibitory antibodies. To test the importance of p185 kinase activity more critically, NIH3T3 cells were transfected with an expression vector containing the full-length human c-erbB-2 gene (cell line 17313), c-erbB-2 with deletion of the kinase region from codons 751-979 (cell line 9309) or c-erbB-2 with deletion of most of the intracellular domain from codons 684-1255 (cell line 9310). Unconjugated antibodies inhibited anchorage-independent growth of 17313 cells as well as SKBr3 cells, but did not inhibit growth of either 9309 or 9310 cells. In contrast, the cytotoxic effect of anti-p185

-ricin A chain (RTA) conjugates was comparable for 17313, 9309 and 9310. The tyrosine-kinase activity of p185 is required for growth inhibition mediated by unconjugated anti-p185 antibodies, but not for the cytotoxic activity of anti-p185-RTA immunotoxins.

L19 ANSWER 4 OF 26 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 97162177 MEDLINE
DOCUMENT NUMBER: 97162177 PubMed ID: 9009164
TITLE: Effects of the tyrosine-kinase inhibitor geldanamycin on ligand-induced Her-2/neu activation, receptor expression and proliferation of Her-2-positive malignant cell lines.
AUTHOR: Hartmann F; Horak E M; Cho C; Lupu R; Bolen J B; Stetler-Stevenson M A; Pfreundschuh M; Waldmann T A; Horak I D
CORPORATE SOURCE: Metabolism Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA.
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AB Geldanamycin belongs to the family of benzoquinoid ansamycin tyrosine-kinase inhibitors. We have examined its effects on Her-2/neu kinase activity, protein expression level, and proliferation of Her-2+ malignant cells. In SK-BR-3 breast-cancer cells, short-time treatment with geldanamycin completely abrogated gp30-ligand-induced activation of Her-2 without a change of receptor-expression level. Longer treatment of intact cells with geldanamycin induced decreased steady-state Her-2 autophosphorylation activity, which correlated with reduction of Her-2 protein expression and phosphotyrosine content of several proteins. The decrease was time- and dose-dependent, starting after 1 hr at 100 nM concentration and reaching completion by 24 hr. The reduction of the Her-2 protein level probably resulted from increased degradation, since the Her-2 mRNA level remained constant. Geldanamycin effects were not specific for Her-2, since the non-receptor tyrosine-kinase fyn was inhibited equally. In contrast to these results, protein-kinase-C activity was not affected. In 3 other malignant cell lines expressing different amounts of Her-2 (SK-BR-3 > SK-OV-3 > OVCAR3 > MCF7), geldanamycin also

effectively reduced Her-2-kinase activity
proportionally to the decrease of protein expression. In contrast, in a [3H]-thymidine-uptake assay, cell growth was meaningfully inhibited by geldanamycin at nanomolar concentrations only in SK-BR-3 (IC50 2 nM) and MCF7 (IC50 20 nM), while OVCAR3 was only moderately sensitive (IC50 2 microM) and SK-OV-3 was clearly resistant to geldanamycin. In direct comparison with herbimycin A, another benzoquinoid ansamycin that has been more thoroughly characterized, the biologic effects of geldanamycin were more pronounced.